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Can malignant lymphadenopathies be predicted? Analysis of clinical, ultrasonographic and laboratory data

Predictive factors for malignant lymphadenopathies

Anar Aslanov, Burak Uçaner, Mehmet Sabri Çiftçi, Mehmet Zeki Buldanlı
Department of General Surgery, University of Health Sciences, Gülhane Training and Research Hospital, Ankara, Turkey

Abstract

Aim: Lymphadenopathy may be result from an infectious disease or manifest an underlying hematologic disease, a metastasis of an as-yet undiagnosed malignancy, or a primary malignancy. This study aimed to investigate whether there is predictive value in malignancy by examining data from patients who underwent excisional biopsy for lymphadenopathy.

Material and Methods: Clinical data from patients who had undergone excisional lymph node biopsy at a single-center approximately six years were retrospectively reviewed. Based on the results of the histopathology report, patients were divided into two separate groups that are malignant and benign histopathology groups. Then, the malignant histopathological group was further divided into two subgroups: primary lymph node malignancy and lymph node metastatic malignancy.

Results: The mean age of patients included in the study was 47.5±17.0 years (19-87 years). It was observed that the CRP levels were higher in primary lymph node malignancies than in metastatic malignancies in lymph nodes (p=0.027). When histopathology results were accepted as a reference, the sensitivity of ultrasonography in detecting malignant lymph nodes was 77.2%, specificity was 48.1%. For malignant lymph nodes, only lymph node diameter proved to be a determinant (p=0.026). Lymph node diameter >25 mm was predictive of malignant histopathology with a sensitivity of 54.5% and a specificity of 66.7%.

Discussion: While ultrasonography is a significant predictor of lymphadenopathy, CRP levels may be important in differential diagnosis of primary lymph node malignancies from metastatic malignancies in the lymph nodes.

Keywords

Lymphadenopathy, Lymphoma, Malignant Lymph Node, Metastatic Lymph Node, Benign Lymph Node

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Corresponding Author: Mehmet Zeki Buldanlı, Department of General Surgery, Gülhane Training and Research Hospital, General Dr. Tevfik Sağlam Street, No:1, 06010, Etlik, Ankara, Turkey.
E-mail: buldanli87@hotmail.com P: +90 312 304 51 50 F: +90 312 304 27 00
Corresponding Author ORCID ID: https://orcid.org/0000-0002-6491-7630
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Introduction

Lymphadenopathy may result from infectious disease or may be an expression of underlying hematologic disease, metastasis of undiagnosed malignancy, or primary malignancy [1]. Histopathologic analysis of the lymph node is necessary for the differential diagnosis of lymphadenopathy in patients [2]. Although imaging-guided fine-needle aspiration biopsy (FNAB) and tru-cut biopsy are the first-choice procedures, these techniques have some disadvantages. FNAB may provide nondiagnostic specimens, while tru-cut biopsy may not provide a diagnosis of diseases such as lymphoma [3]. The European Society of Medical Oncology (ESMO) guidelines recommend an excisional biopsy of lymph nodes to diagnose and type lymphoma [4]. According to these guidelines, the chance of early diagnosis and treatment is higher in palpable lymph nodes thanks to imaging-guided and excisional biopsies [4].

In this study, we aimed to examine in detail the preoperative, intraoperative, and postoperative data of patients who underwent excisional biopsy for lymphadenopathy approximately six years, compare the results, and investigate whether there is predictive value in terms of malignancy and whether it is a predictor that distinguishes primary lymph node malignancies.

Material and Methods

Patients older than eighteen years of age and who underwent excisional lymph node biopsy for lymphadenopathy from October 2016 to June 2022 in a single tertiary hospital were included in this retrospective study. Patients younger than 18 years, patients with a previous malignancy diagnosis, and patients who had undergone surgical procedures such as lymphadenectomy and lymph node dissection additional for main surgery were excluded from the study. In this study, patient demographics such as age and gender, American Society of Anesthesiologists scores, symptoms, comorbidities, clinical data such as length of hospital stay, intensive care unit (ICU) stay status, preoperative ultrasonography (US) and laboratory results, and Clavien-Dindo Classification System results for postoperative complications, reoperation status and histopathological report results were examined. Preoperative laboratory results of white blood cell counts (WBC, 10^3/µl), hemoglobin levels (Hb, g/dl), neutrophil counts (Neu, 10^3/µl), lymphocyte counts (Lym, 10^3/µl), platelet counts (Plt, 10^3/µl), lactate dehydrogenase levels (LDH, 10^3/µl), C-reactive protein levels (CRP, mg/l) and albumin levels (Alb, g/dl) were analyzed. Imaging results included lymph node size in US reports and the radiologist's reactive or pathologic description of the lymph node.

Based on the results of the histopathology report, patients were divided into two separate groups that are malignant and benign histopathology groups. Then, the malignant histopathological group was further divided into two subgroups, namely primary lymph node malignancy and lymph node metastatic malignancy. This study was conducted under the fundamental ethical principles for medical research involving human subjects, as stated in the guidelines of the World Medical Association Declaration of Helsinki, and was approved by the local ethics committee (01.07.2022-2022/103).

Statistical analysis

Statistical analyzes were performed using the SPSS package program version 22.0. Descriptive statistics were expressed as a number, percentage, mean and standard deviation, and median. The conformity of variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods ("Kolmogorov–Smirnov," "Shapiro-Wilk"). Normally distributed numerical variables were analyzed between the two groups using the "T-test in independent groups," and numerical variables that did not have a normal distribution were analyzed between the two groups using the "Mann Whitney U test" "Chi-square" and "Fisher's Exact test" were preferred for comparing nominal data. Analysis of predictive factors for malignant histopathology was evaluated using the "ROC (receiver operating characteristic) analysis." The ROC Analysis was expressed as the area under the curve (AUC) with a 95% confidence interval (CI). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the threshold determined with the "Youden index" in the ROC analysis. In the study's statistical analysis, comparisons with a P value less than 0.05 were considered statistically significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The mean age of the 120 patients included in the study was 47.5±17.0 years (19-87 years). Sixty-three patients were female, and 57 patients were male. The female-to-male ratio was 1.1/1. In 56.7% of the patients, there was a comorbidity other than malignancy. Symptoms were present in 81.7% of patients. The most common symptoms were a palpable mass

Table 1. Patient characteristics

Characteristics	Number	Percent
Gender		
Female	63	52.5
Male	57	47,5
ASA		
I	33	27.5
II	78	65
III	9	7.5
Presence of comorbidity	68	56.7
Presence of symptom	98	81.7
Palpable mass	84	70
Pain	21	17.5
Weight loss	3	2.5
Sweating	4	3.3
Fever	2	1.7
Other	6	5.0
Lymph node localization		
Axillary	78	65
Inguinal	26	21.7
Cervical	10	8.3
Supraclavicular	3	2.5
Intraabdominal	2	1.7
Femoral	1	0.8
Ultrasonographic description		
Pathologic	79	65.8
Reactive	41	34.2

ASA: American Society of Anesthesiologists

(70%) and pain (17.5%). Lymphadenopathies were most commonly observed in the axillary (65%), inguinal (21.7%), and neck (8.3%) regions. The US finding was a pathological lymph node in 65.8% of patients. The median size of the lymph nodes was 25 (5-83) mm. The median length of hospital stay was one day (0-9 days). None of the patients required reoperation. In addition, according to the Clavien-Dindo classification, no complications were observed in the patients. Only one patient required intensive care unit stay (Table 1).

The histopathologically malignant and benign lymph nodes were compared in terms of demographic and clinical features. The diameter of lymph nodes in malignant histopathology was significantly larger (p=0.029). In addition, malignant lymph nodes were more frequently reported that pathological lymph nodes on US (p=0.003) (Table 2). When histopathology results were accepted as a reference, the sensitivity of US in detecting malignant lymph nodes was 77.2%, specificity was 48.1%, PPV was 64.5%, and NPV was 63.4%.

The histopathology of malignant and benign lymph nodes was compared in terms of preoperative laboratory results, and no significant difference was found.

Malignant lymph nodes were divided into primary and lymph node metastatic malignancies, and the demographic and clinical characteristics were compared between the groups, but no significant difference was found.

The primary and metastatic lymph node groups were compared in terms of preoperative laboratory results. It was found that CRP levels were higher in primary lymph node malignancies (p=0.027) (Table 3).

Parameters potentially determinant in malignant lymph nodes were evaluated with ROC analysis. In malignant lymph nodes, only lymph node diameter proved to be a determinant (AUC = 0.616, 95% CI 0.523-0.703, p=0.026). Lymph node diameter greater than 25 mm was predictive of malignant histopathology, with a sensitivity of 54.5%, specificity of 66.7%, PPV of 66.7% and NPV of 54.5%.

Table 2. Comparison of malignant and benign lymph nodes in terms of demographic and clinical characteristics.

Characteristics	Group B (n=54) n (%)	Group M (n=66) n (%)	p value
Age*	45.3±17.2	49.3±16.8	0.201†
Gender			0,180††
Female	32 (59.3)	31 (47)	
Male	22 (40.7)	35 (53)	
ASA			0.480††
I	17 (31.5)	16 (24.2)	
II	32 (59.3)	46 (69.7)	
III	5 (9.3)	4 (6.1)	
Presence of comorbidity	30 (55.6)	38 (57.6)	0.824††
Presence of symptom	45 (83.3)	53 (80.3)	0.670††
Palpable mass	37 (68.5)	47 (71.2)	0.749††
Pain	12 (22.2)	9 (13.6)	0.218††
Lymph node localization			
Axillary	39 (72.2)	39 (59.1)	0.134††
Inguinal	12 (22.2)	14 (21.2)	0.894††
Cervical	2 (3.7)	8 (12.1)	0.182‡
Ultrasonographic description			0.003††
Pathologic	28 (51.9)	51 (77.3)	
Reactive	26 (48.1)	15 (22.7)	
Lymph node diameter (mm)**	22 (5-83)	26,5 (9-70)	0.029‡‡
Length of hospital stay (days)**	1 (0-3)	1 (0-9)	0.791‡‡

*Mean±Standard deviation, **Median (minimum-maximum), †T test in independent groups, ††Chi-square test, ‡Fisher Exact test, ‡‡Mann Whitney U test, ASA: American Society of Anesthesiologists.

Table 3. Comparison of primary and metastatic lymph nodes in malignant lymph nodes in terms of laboratory results.

	Group PLNM (n=52) Median (minimum-maximum)	Group LNMM (n=14) Median (minimum-maximum)	p value
White blood cell (10^3/µl)	8.3 (2.2-51.1)	6.7 (3.4-9.8)	0.269*
Hemoglobin (g/dl)*	13.4±1.7	13.9±1.8	0.345††
Neutrophil (10^3/µl)	56.9 (8.1-85.5)	60.9 (36.7-74.8)	0.315*
Lymphocyte (10^3/µl)	31.6 (8.5-90.2)	28.9 (13.9-49)	0.410*
Platelet (10^3/µl)	244 (42-735)	269 (212-372)	0.246*
Lactate dehydrogenase (10^3/µl)	208 (137-583)	175 (137-247)	0.079*
C-Reactive Protein (mg/l)	2.1 (0.1-285)	0.1 (0.1-12.3)	0.027*
Albumin (g/dl)*	4.1±0.5	3.9±0.5	0.216††

*Mean±Standard deviation, *Mann Whitney U test, ††T test in independent groups, PLNM: Primary Lymph Node Malignancy; LNMM: Lymph Node Metastatic Malignancy

Discussion

Peripheral lymphadenopathy is a secondary condition in malignant, hematologic, or infectious disease and may require excisional lymph node biopsy, a procedure generally included in the diagnostic algorithm. Because of excisional lymph node biopsy is a surgical procedure, FNAB and tru-cut biopsy, less invasive techniques, have come to the forefront. However, excisional lymph node biopsy remains highly actual due to poor diagnostic performance, reintervention, and the fact that it cannot be performed in every center [5]. In this study, all patients underwent excisional lymph node biopsy for diagnostic purposes.

It is known that there are many lymph node regions in the human body. Peripheral lymph node localizations, especially in the neck and groin area, may be painful and palpable after a rapid growth tendency due to infectious diseases. In such cases, the lymph nodes may decrease in size due to etiology-targeted treatment with anti-inflammatory, antiviral, or antibiotic agents and regression of existing pathology, symptoms may resolve, and biopsy is usually not required [6].

However, lymphadenopathies that develop secondary to malignant or hematologic pathologies may enlarge. In addition to their size, they do not regress and may be painless. Also, the risk factors for malignancy include the white race, age older than 40 years, male gender, supraclavicular lymphadenopathy, and systemic symptoms such as fever, night sweats, unexplained weight loss has been described. In these cases, the first diagnostic option in the algorithm may be needle biopsy. However, the gold standard in diagnosis is excisional biopsy [7, 8].

In the diagnosis of malignant lymph nodes, laboratory tests are performed before excisional lymph node biopsy to establish the diagnosis. Among laboratory parameters, acute phase reactants such as WBC, CRP, and erythrocyte sedimentation rate

take precedence. In addition, parameters such as neutrophils, monocytes, and lymphocytes may be used for bacterial, parasitic, and viral infectious etiology. While immunoglobulins, lactate dehydrogenase, autoantibodies, and platelets can be used for hematologic and rheumatologic etiologies, biomarkers can also be used for malignancies [9-11]. No statistically significant difference was found between the benign and malignant groups in the laboratory parameters examined in this study. However, it was observed that CRP levels were significantly higher in the group with primary malignant lymph nodes.

There are differences between imaging modalities regarding diagnostic performance in recognizing lymph nodes as pathological. While the US is superior in the inguinal, cervical, and axillary regions, cross-sectional examinations such as computed tomography (CT) and magnetic resonance imaging (MRI) are more prominent in the intraabdominal, retroperitoneal, and mediastinal regions [12].

The advantages of the US, such as the fact that it is inexpensive, easily accessible, radiation-free, and simple to use, also support its usage in diagnostics. Pathologic description in the radiologist's ultrasonography report, which can be considered a predictor of malignant histopathology, depends on certain criteria. The lobular contour structure of the lymph node, the decrease in the ratio of longitudinal to transverse size, the presence of necrosis, the absence of an echogenic hilus, and the increase in lymph node diameter are the findings support the pathologic condition. In addition, peripheral and mixed blood supply on coloured Doppler US may be significant for malignancy [13, 14]. In this study, the pathologic description of the lymph node was radiologically significant between groups in favor of the malignant histopathologic group.

The pathologic assumption of lymph node enlargement may show regional differences. When considering adult dimensions after adolescence, the histopathological diagnosis may arise with lymph nodes larger than 1 cm. In the literature, lymph nodes larger than 1.5 cm in the inguinal and mediastinal regions, 1 cm in the cervical and axillary regions, and 2 cm in the intraabdominal region are considered abnormal, and in general, lymph nodes larger than 2.5 cm are reported to have a seriously increased risk of malignancy [15, 16]. In this study, the lymph node diameter was found to be important for the malignant histopathology group. Moreover, when evaluating the parameters that could be determinant for malignant lymph nodes, it was found with ROC analysis that only the lymph node diameter was determinant.

Study limitations

This study's limitations were the retrospective design of the study, the limited number of patients, and the inability to evaluate parameters such as biomarkers in laboratory data because of the insufficient number of patients when the data were examined. In addition, the lack of sufficient patient data on cross-sectional imaging studies such as CT and MRI was another study limitation.

Conclusion

Imaging and laboratory tests are essential to clarify the etiology after an effective anamnesis and physical examination when persistent lymphadenopathy is detected. US can provide very valuable information for predicting malignancy. High levels of CRP value can predict the differential diagnosis between a primary malignant lymph node and a metastatic lymph node. However, there is a need for randomized, prospective studies and reviews with a larger patient population on this topic.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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